Respiratory Medicine (2009) **103**, 1816–1821

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/rmed

Prognostic value of the 6 min walk test in bronchiolitis obliterans syndrome

Steven D. Nathan*, Oksana A. Shlobin, Erika Reese, Shahzad Ahmad, Margaret Fregoso, Chanda Athale, Scott D. Barnett

Advanced Lung Disease and Lung Transplant Program, Inova Fairfax Hospital, Falls Church, VA, United States

Received 27 February 2009; accepted 19 July 2009
Available online 13 August 2009

KEYWORDS
Lung transplantation;
Exercise testing;
Bronchiolitis obliterans syndrome;
Graft rejection

Summary
Bronchiolitis Obliterans Syndrome (BOS) complicates the course of many lung transplant recipients. It carries significant risk of morbidity and mortality, but its course is difficult to characterize. We evaluated the prognostic utility of the 6 min walk test (6MWT) obtained after the onset of BOS in 42 patients. This was compared to the prognostic significance of changes in the FEV_1. The median time between the onset of BOS and the 6MWT was 109 days. The median decline in the FEV_1 from baseline to BOS onset was 25.7%, while the median change over the ensuing 3 months was 12.5%. Neither of these was predictive of subsequent mortality. The 6MWT yielded averages in the resting saturation, lowest saturation, distance walked and maximal Borg scores of 97%, 90.2%, 323 m and 2.35, respectively. The best of these parameters in discriminating survival was the distance. Patients who walked further than 330 m had a median survival of 1178 days versus 263 days for those who walked less ($p < 0.0001$). We conclude that the 6MWT provides important prognostic information in patients with BOS and might perform better than spirometry. Use of this test might allow different clinical phenotypes to be discerned.

Introduction

Lung transplantation is a therapy that is reserved for patients with certain types of advanced lung disease who have failed all other forms of therapy.[1] It is fraught with the potential for a multitude of complications including chronic rejection.[2,3] The pathologic correlate of chronic rejection is thought to be bronchiolitis obliterans (BO). There are no proven effective therapies for BO and management is geared towards its prevention and early detection. The diagnosis of BO usually requires a surgical lung biopsy since transbronchial biopsies lack sufficient sensitivity to suffice as a diagnostic tool. To avoid subjecting patients to unnecessary biopsies when the *a priori* suspicion is high for

* Corresponding author. Director, Advanced Lung Disease and Transplant Program, Inova Fairfax Hospital, Falls Church, VA 22042, United States. Tel.: +1 703 776 3610; fax: +1 703 776 3515.
E-mail address: steven.nathan@inova.org (S.D. Nathan).

0954-6111/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.rmed.2009.07.011

BO, the International Society for Heart and Lung Transplantation (ISHLT) defined the physiologic entity of bronchiolitis obliterans syndrome (BOS) in 1993, with a subsequent update published in 2002.[4,5] BOS is defined by a permanent 20% reduction in the patients' FEV_1 from their prior baseline without other apparent cause. This baseline is defined as the average of the two highest FEV_1s obtained at least 3 weeks apart.

There is now a growing recognition of different BOS phenotypes with varying onsets, course, and prognoses.[6–9] BOS has also been characterized by different airway and bronchoalveolar lavage (BAL) cellular expression.[10–13] It is highly likely that BOS encompasses a number of different entities and potentially different etiologies, some of which may be immunologic and others non-immunologic.[14] Different physiologic phenotypes have also previously been described, but these have been mostly based on patients' pulmonary function changes, specifically the FEV_1.

The 6 min walk test (6MWT) has been used in many different forms of advanced lung disease to define the functional ability of patients, assess their oxygen needs and has also been found to be useful in discerning prognosis.[15–18] Determining the prognosis of BOS is very important for patient counseling and disease management. We therefore attempted to assess the prognostic utility of the 6MWT in lung transplant recipients with BOS and to compare this to the commonly used FEV_1 in determining subsequent outcomes.

Methods

We performed a retrospective analysis of serial pulmonary function tests (PFTs) and 6MWTs in lung transplant recipients who developed BOS in the time period from 2000 to 2006. The goal of the study was to assess the prognostic utility of the 6MWT in patients who developed BOS during the defined study period. The study group therefore included patients transplanted in the 6 years time frame, but also included patients transplanted prior to 2000 if they met BOS criteria during the study period.

Our lung transplant programs protocol mandates that patients be seen as outpatients weekly for the first month after discharge, biweekly for 2 months and then monthly for the first year. After the first year, they are seen every third month or more often if clinically indicated. All patients have spirometry performed with each clinic visit. The prediction equations of Knudsen et al. are used for all spirometric maneuvers which are performed per the American Thoracic Society (ATS) standards.[19] For the purposes of this study, chronic allograft dysfunction (CAD) was defined by patients meeting BOS physiologic criteria, with or without a new radiographic pleuroparenchymal process. BOS was defined according to the ISHLT recommendations; specifically patients had to have a permanent 20% or greater reduction in the FEV_1 from the prior established baseline in the absence of an identifiable cause, including any restrictive process.[5] Patients were categorized based on their initial BOS-qualifying FEV_1 into stage 1 (FEV_1 65–79% of baseline), stage 2 (FEV_1 50–64% of baseline) or stage 3 ($FEV_1 < 50\%$ of baseline) BOS. Changes in the patients' PFTs over the 3 months post-BOS onset were also assessed.

After patients qualify as having BOS, a 6MWT is obtained to assess patient's functional status and the possible need for oxygen therapy. All patients are walked on room air unless their resting oxygen saturation is <88%. In such cases, they are placed on oxygen which is then titrated up during the course of the 6MWT to maintain a saturation of >90%. The following data was extracted from the 6MWT after the onset of BOS: the distance walked, the baseline oxygen saturation (SpO_2baseline), the lowest oxygen saturation (SpO_2 nadir) and the maximal Borg dyspnea score during the walk. In addition, the distance-saturation product (DSP) was calculated. This is the product of the lowest oxygen saturation expressed as a fraction and the distance walked.[20]

The primary endpoint of the study was patient mortality. This was discerned from our Program's lung transplant database and the Social Security Death Index. The severity of BOS at the time of its onset was assessed as a predictor of survival. Parameters from the initial 6MWT obtained after patients had qualified as having BOS were also assessed as predictors of subsequent mortality. These included the distance walked, the maximal Borg score, the SpO_2baseline, SpO_2nadir and the SpO_2 change. The study was approved by the Hospital Institutional Review Board.

Statistics

Continuous data are presented as mean and range or standard deviation. Categorical data are presented as frequency and percent. Cumulative probability of death after post-bronchiolitis obliterans syndrome was calculated using Kaplan–Meier curves with significance testing by the log-rank test. Cox proportional hazard modeling was utilized to generate hazard ratios (HR) and 95% confidence intervals (CI) to assess the association of select PFTs and 6MWT data on patient survival. This modeling was performed using categories of 50 m for the walk distance and 10% for the FEV_1. All statistical analyses were conducted using GraphPad Prism (Version 4.0, San Diego CA) and SAS 9.2 (Carey, NC).

Results

In the 6 years time period of the study, there were 43 patients who developed chronic allograft dysfunction as defined by a permanent 20% or greater reduction in the FEV_1 in whom there was 6MWT data available after the diagnosis was established. The diagnosis of BOS was confirmed in 42/43 patients by reviewing their radiographic studies at the time of diagnosis. Specifically, at the time of diagnosis, patients either had a clear chest X-ray (CXR) and/or CAT scan ($N = 35$) or an old stable radiographic abnormality ($N = 7$). Only one of the 43 patients had new progressive interstitial infiltrates and therefore was not regarded as having BOS. Of the 42 patients, there were 7 bilateral (BLTx) and 35 single lung transplant recipients (SLTx). The demographics of the final cohort are shown in Table 1.

The time interval from transplant to the first of the two sets of PFTs that defined their baseline FEV_1 was 408 days (range: 18–1472 days). The time interval from attaining their

Table 1 Demographics of the study cohort.

	$N = 42$
Age (years), mean ± SD	53.1 ± 11.2
Female, *N* (%)	17 (40.5)
Caucasian *N* (%)	33 (78.6)
Primary disease *N* (%)	
IPF	24 (57.1)
COPD	9 (21.4)
Sarcoidosis	5 (11.9)
Other	4 (9.5)
Bilateral lung recipient *N* (%)	7 (16.7)
Single lung recipient *N* (%)	35 (83.3)
Baseline FEV_1% predicted	70.7 ± 19.9
Baseline FVC % predicted	70.6 ± 19.6
Time to BOS (years)	3.3 ± 1.9

maximal lung function to the onset of BOS was 758 days (range: 69–2546 days). The average baseline FVC was 2.78 ± 0.91 (70.9 ± 19.6%) and the FEV_1 was 2.25 ± 0.70 (70.8 ± 19.39%). For the SLTx patients, the baseline FVC was 2.63 ± 0.8 L (70.1 ± 20.18%) and the FEV_1 was 2.09 ± 0.58 (69.08 ± 19.14%), while for the BLTx recipients it was 3.55 ± 1.08 (75 ± 17%) and 3.00 ± 0.80 (79.6 ± 19.56%), respectively.

The median decline in the FEV_1 from the baseline that defined the onset of BOS was 25.71%. The majority of patients (34/42 or 81%) qualified as BOS stage 1, while 5 (12%) and 3 (7%) patients qualified as BOS stages 2 and 3, respectively. Since most patients had BOS stage 1 at the time of BOS onset, comparison of groups was performed by combining BOS stages 2 and 3. BOS stage at the time of BOS onset was not predictive of subsequent survival (Fig. 1). When patients were dichotomized by the median change in the FEV_1, this similarly did not discriminate subsequent survival ($p < 0.76$). Changes in the patient's FEV_1 over the 3 months post-BOS onset also did not discriminate survival. The median decrement in the FEV_1 for the 3 months period after the diagnosis of BOS was 12.5% and the survival for those patients above and below this threshold is shown in Fig. 2.

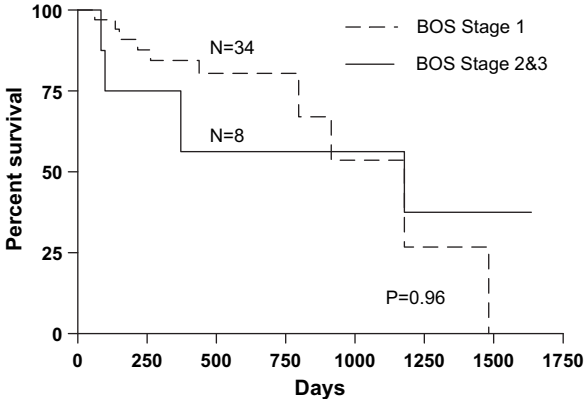

Figure 1 Comparison of outcomes between patients with initial BOS stage 1 and those with initial BOS stage 2 or 3.

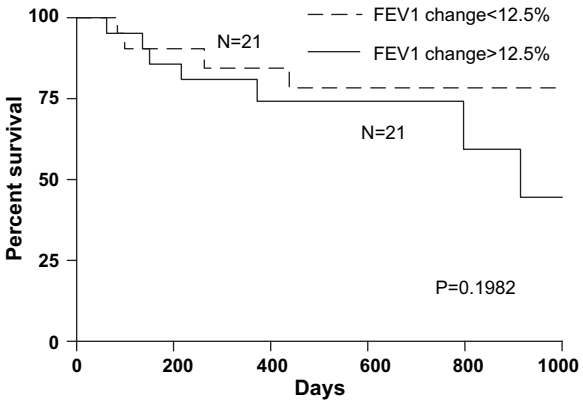

Figure 2 Outcomes for those patients with BOS who had a >12.5% decrement in their FEV_1s compared to those whose subsequent FEV_1 decline was <12.5% in the 3 months after the onset of BOS.

The mean time interval between the onset of BOS and the first 6MWT performed thereafter was 109 days (range:0–734), while the median time was 43 days. Apart from one patient, all the patients were walked on room air. The one patient who had a resting oxygen saturation < 88% was walked on 2 L/min via nasal cannula. The average resting saturation, lowest saturation, distance walked and maximal Borg scores at the time of BOS diagnosis were 97.04 ± 2.08%, 90.21 ± 5.27%, 322.88 ± 118.8 m and 2.35 ± 1.95, respectively. The distance walked correlated with subsequent survival. The median 6MWT distance for the group was 340 m. Those patients who walked further than this had a median survival of 1178 days compared to 438 days for those who walked less ($p < 0.001$) (Fig. 3). The best cut point to discern survival appeared to be a 6MWT distance of 300 m. For those patients who walked further, the median survival was 1178 days versus 263 days for those who walked less ($p < 0.0002$). The 1 year survival for patients who walked >300 m was 100% versus 38.46% for those who walked <300 m ($p < 0.01$). Oxygen saturation at baseline, the degree of desaturation and the lowest oxygen saturation did not appear to discern subsequent survival. The best performing of these parameters was desaturation

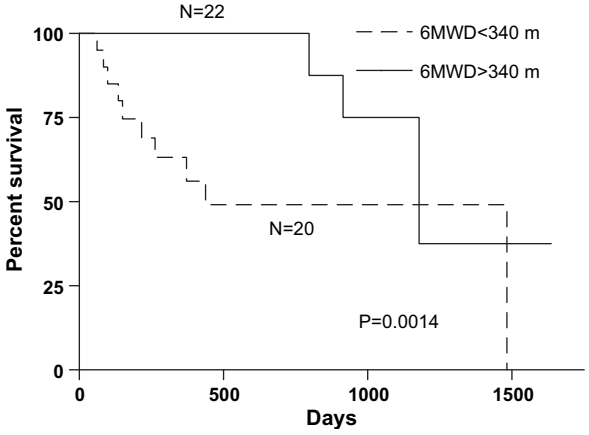

Figure 3 Survival of BOS patients based on the initial 6MWT distance dichotomized by the median distance of 340 m.

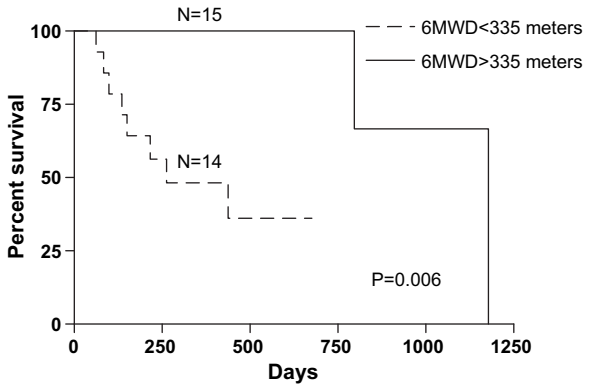

Figure 4 Survival of BOS patients with 6MWT data available within 3 months of BOS diagnosis, dichotomized by the median distance of 335 m.

to <89% during the 6MWT which still failed to reach significance in discriminating survivors from non-survivors ($p < 0.10$). The DSP did not perform any better than the distance alone.

A subgroup analysis was performed of those patients who had 6MWT data within 3 months after the onset of BOS. Twenty-nine patients met this criterion with similar results to the entire cohort. The median 6MWT distance was 335 m. Those patients who walked less than this had a median survival of 263 days compared to 1178 days for those who walked further (Fig. 4). The SpO_2 nadir for this subgroup did correlate with survival; those patients who desaturated <90% had a median survival of 438 days compared to 1178 days for those whose SpO_2 remained ≥90% during the 6MWT ($p < 0.034$) (Fig. 5). The DSP performed equivalently to the 6MWT distance; the median DSP of the subgroup was 300 which discerned the same patients as the 6MWT distance of 335 m.

Proportional hazards modeling using 50 m increments revealed a significant protective effect for distance achieved during the 6MWT (HR: 0.63; 95% CI: 0.45—0.87) but no association was observed for the change in FEV_1 (using 10% decrements) from baseline to BOS diagnosis and survival (HR: 1.05; 95% CI: 0.67—1.66). Similarly, there was no association observed between the subsequent change in FEV_1 over the 3 months after BOS onset and survival (HR: 1.23; 95% CI: 0.89—1.71). When the 6MWT distance was dichotomized by the median distance, patients with a distance < 340 m were at a significantly increased risk of death (HR: 6.29; 95% CI: 1.88—21.03). This increased risk of death remained significant despite adjustment for the change in FEV_1 from baseline to BOS diagnosis (HR: 6.04; 95% CI: 1.78—20.51). When the monthly change in FEV_1 was dichotomized by the median of 12.5%, patients with > 12.5% change in FEV_1 were not found to be at increased risk of mortality (HR: 1.14; 95% CI: 0.34—3.76) despite adjustment for 6MWT distance (HR: 5.96; 95% CI: 1.62—21.96).

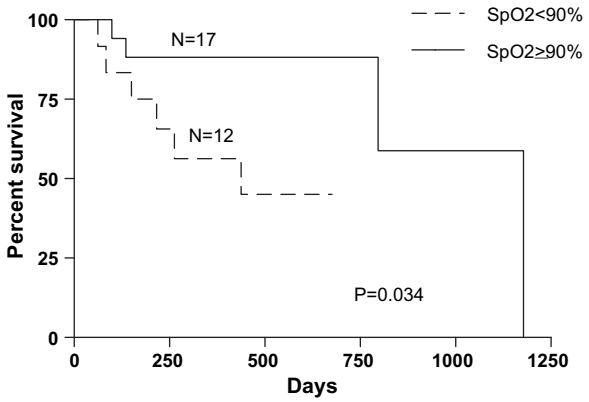

Figure 5 Survival of BOS patients with 6MWT data available within 3 months of BOS diagnosis, dichotomized by those who desaturated to <90% during the 6MWT compared to those whose lowest oxygen saturation remained ≥90%.

Discussion

Bronchiolitis obliterans syndrome (BOS) complicates the course of many patients after lung transplantation. It is the major cause of morbidity and mortality beyond the first year after transplantation. We demonstrate that data from the 6MWT obtained soon after the diagnosis of BOS provides important prognostic information. Of the parameters assessed, the distance walked appeared to impart the best prognostic information as demonstrated by Kaplan—Meier survival analysis as well as Cox proportional hazards modeling.

It is commonly held that BO is the pathologic correlate of chronic allograft rejection.[2] There is no proven effective therapy for BOS and management is usually directed towards its prevention, as well as augmenting immunosuppression and minimizing complications, such as infections.[2] BOS can have a highly variable course with different clinical patterns of presentation and progression having been reported.[6—9] Patients have also been categorized based on bronchoalveolar lavage neutrophilia.[10—13] It is not clear that all cases of BOS are BO and that all BO is necessarily immunologically related.[14] Therefore it is becoming increasingly important to recognize different BOS phenotypes, not only for prognostic purposes, but also in the design and implementation of clinical treatment trials.

The 6MWT has been used extensively as a simple non-invasive measure of patients' functional status and to provide an assessment of oxygen needs with activity. It has also since been found to impart important prognostic information in many forms of advanced lung disease.[16—18] In this regard, the 6MWT has been suggested to be more useful than standard PFT measurements in a number of disease conditions.[20—22]

The 6MWT has also been used commonly in potential lung transplant recipients and for this broad category of patients has been found to be an important prognostic indicator. Indeed the distance walked has been incorporated in the United Network for Organ Sharing (UNOS) lung allocation score for all listed lung transplant candidates. It has not as yet however been assessed as a prognostic indicator in patients post-lung transplantation. To our knowledge, this is the first report of the prognostic utility of the 6MWT in patients who develop BOS post-lung transplantation. We demonstrate that it provides more accurate prognostic information than the commonly used FEV_1 or changes in the FEV_1 over the 3 months post-BOS onset. It is the distance component of the 6MWT that appears to provide the best prognostic information. The SpO_2 nadir did not appear to add

further prognostic information although this was also significantly associated with outcomes. The distance-saturation product also did not improve the prognostic accuracy over the distance alone.

It is not altogether surprising that the 6MWT performs better than PFT parameters since this has previously been demonstrated in other forms of advanced lung disease. Rather than a single static lung volume measurement, the 6MWT has the advantage of providing a global assessment of patient's functional status and therefore enables the effects of other comorbidities to be accounted for. For example, patients with BOS might develop associated pulmonary hypertension or diastolic dysfunction which might impact on their prognosis and 6MWT, but might not be captured by changes in the FEV_1. Furthermore, those patients who are functionally impaired from other comorbidities are more likely to have poorer outcomes. Similar to what is seen in COPD, there may be a subgroup of patients with BOS, who have very low FEV_1s, but might otherwise survive for many years.[23] This group may be differentiated by their relatively well-preserved functional status. One entity that might cause such a physiologic scenario is bronchomalacia which can be seen in lung transplant recipients but which might not be discernable from BO based on PFT changes alone.[24,25] Post-transplant 6MWTs might have an important role in the decision making process with regards to retransplantation among those select recipients who are appropriate candidates. It appears that a distance of 300–335 m might be especially useful in determining the optimal timing of listing for retransplantation. Specifically, those who walked more demonstrated a greater one year survival, while those who walked less did significantly worse than might be expected with a retransplant.

It appears therefore that the 6MWT is a valuable clinical prognostic adjunct that should be assessed in all patients with BOS. It does allow physiologic phenotypes with distinctly different outcomes to be identified. Whether these physiologic phenotypes correlate with different etiologic, pathologic or cellular/cytokine entities remains to be determined. The prognostic value of the 6MWT also has implications with regards to potential contributory components to mortality in patients with BOS. Specifically, systemic effects, deconditioning and other comorbidities may all play important roles.

Our study has a few limitations. First, not all patients had 6MWT assessed in a standardized temporal fashion after the onset of BOS. Therefore the 6MWTs that were analyzed were obtained at varying time intervals after the onset of BOS. However, our subgroup analysis of those patients with 6MWT within 3 months of BOS onset provided similar results with regards to the prognostic value of the distance walked. Indeed, although the numbers were smaller in this subgroup, the SpO_2 nadir did reach significance whereas it was not a significant predictor in the larger group with the longer temporal intervals. Also, the 6MWT performed within 3 month of BOS onset performed better as a prognostic tool in comparison to spirometry. Moreover, it also outperformed the change in the FEV_1 over the 3 month period from BOS onset. This underscores the superiority of the 6MWT over spirometry in discerning outcomes.

In conclusion, our study demonstrates that the 6MWT imparts important prognostic information in lung transplant recipients who develop BOS. This simple test of functionality might perform better in this regard than standard pulmonary function measures. Although the FEV_1 defines the onset of BOS, it appears important to obtain a 6MWT in all such patients as this will provide important information about the possible need for oxygen as well as counseling with regards to expected outcomes. The 6MWT might also be important in the design and implementation of strategies for the prevention of BOS and future studies of potential therapies.

Conflict of interest statement

None of the authors have any financial or other conflicts of interest to declare with regards to the subject matter of this paper.

Acknowledgement

The authors would like to acknowledge the valuable input and assistance of Dr. Steven M. Kawut in reviewing this paper.

References

1. Orens JB, Estenne M, Arcasoy S, Conte JV, Corris P, Egan JJ, Egan T, Keshavjee S, Knoop C, Kotloff R, Martinez FJ, Nathan S, Palmer S, Patterson A, Singer L, Snell G, Studer S, Vachiery JL, Glanville AR. International Guidelines for the Selection of Lung Transplant Candidates: 2006 Update — A Consensus Report From the Pulmonary Scientific Council of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant* 2006;**25**:745–55.
2. Estenne M, Hertz MI. Bronchiolitis obliterans after human lung transplantation. *Am J Respir Crit Care Med* 2002;**166**:440–4.
3. Al-Githmi I, Batawil N, Shigemura N, Hsin M, Lee TW, He GW, Yim A. Bronchiolitis obliterans following lung transplantation. *Eur J Cardiothorac Surg* 2006;**30**:846–51.
4. Cooper JD, Billingham M, Egan T, Hertz MI, Higenbottam T, Lynch J, Mauer J, Paradis I, Patterson GA, Smith C. A working formulation for the standardization of nomenclature and for clinical staging of chronic dysfunction in lung allografts. International Society for Heart and Lung Transplantation. *J Heart Lung Transplant* 1993;**12**(5):713–6.
5. Estenne M, Maurer JR, Boehler A, Egan JJ, Frost A, Hertz M, Mallory GB, Snell GI, Yousem S. Bronchiolitis obliterans syndrome 2001: an update of the diagnostic criteria. *J Heart Lung Transplant* 2002 Mar;**21**:297–310.
6. Jackson CH, Sharples LD, McNeil K, Stewart S, Wallwork J. Acute and chronic onset of bronchiolitis obliterans syndrome (BOS): are they different entities? *J Heart Lung Transplant* 2002;**21**(6):658–66.
7. Brugiere O, Pessione F, Thabut G, Mal H, Jebrak G, Leseche G, Fournier M. Bronchiolitis obliterans syndrome after single-lung transplantation: impact of time to onset on functional pattern and survival. *Chest* 2002;**121**(6):1883–9.
8. Nathan SD, Ross DJ, Belman MJ, Shain S, Elashoff JD, Kass RM, Koerner SK. Bronchiolitis obliterans in single-lung transplant recipients. *Chest* 1995;**107**(4):967–72.
9. Lama VN, Murray S, Lonigro RJ, Toews GB, Chang A, Lau C, Flint A, Chan KM, Martinez FJ. Course of FEV_1 after onset of

bronchiolitis obliterans syndrome in lung transplant recipients. *Am J Respir Crit Care Med* 2007;**175**:1192—8.
10. Zheng L, Whitford HM, Orsida B, Levvey BJ, Bailey M, Walters EH, Williams TJ, Kotsimbos T, Snell GI. The dynamics and associations of airway neutrophilia post lung transplantation. *Am J Transplant* 2006;**6**:599—608.
11. Zheng L, Walters EH, Ward C, Wang N, Orsida B, Whitford H, Williams TJ, Kotsimbos T, Snell GI. Airway neutrophilia in stable and bronchiolitis obliterans syndrome patients following lung transplant. *Thorax* 2000;**55**:53—60.
12. Riise GC, Anderssion BA, Kjellstrom C, Martensson G, Nilsson FN, Ryd W, Schersten H. Persistent high BAL fluid granulocyte activation marker levels as early indicators of bronchiolitis obliterans after lung transplant. *Eur Respir J* 1999;**14**:1123—30.
13. DiGiovine B, Lynch III JP, Martinez FJ, Flint A, Whyte RI, Iannettoni MD, Arenberg DA, Burdick MD, Glass MC, Wilke CA, Morris SB, Kunkel SL, Strieter RM. Bronchiolitis lavage neutrophilia is associated with obliterative bronchiolitis after lung transplantation. *J Immunol* 1996;**157**:4194—202.
14. Martinu T, Howell DN, Davis RD, Steele MP, Palmer SM. Pathologic correlates of bronchiolitis obliterans syndrome in pulmonary retransplant recipients. *Chest* 2006;**129**:1016—23.
15. ATS Committee on Proficiency Standards for Clinical Function Laboratories. ATS Statement:Guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002;**166**:111—7.
16. Miyamoto S, Nagaya N, Satoh T, Kyotani S, Sakamaki F, Fujita M, Nakanishi N, Miyatake K. Clinical correlates and prognostic significance of six-minute walk test in patients with primary pulmonary hypertension. Comparison with cardiopulmonary exercise testing. *Am J Respir Crit Care Med* 2003;**161**:487—92.
17. Lama VN, Flaherty KR, Toews GB, Colby TV, Travis WD, Long Q, Murray S, Kazerooni EA, Gross BH, Lynch JP, Martinez FJ. Prognostic value of desaturation during a 6-minute walk test in idiopathic interstitial pneumonia. *Am J Respir Crit Care Med* 2003;**168**:1084—90.
18. Celli BR, Cote CG, Marin JM, Casanova C, Montes de Oca M, Mendez RA, Plata VP, Cabral HJ. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med* 2004;**350**:1005—12.
19. American Thoracic Society Statement. Lung function testing: selection of reference values and interpretative strategies. *Am Rev Respir Dis* 1991;**144**:1202—18.
20. Lettieri CJ, Browning RF, Shorr AF, Ahmad S, Nathan SD. The distance saturation product: a novel measure for mortality prediction in idiopathic pulmonary fibrosis. *Respir Med* 2006; **100**:1734—41.
21. Shorr AF, Davies D, Nathan SD. Outcomes for patients with sarcoidosis awaiting lung transplantation. *Chest* 2002;**122**: 233—8.
22. Cote CG, Pinto-Plata V, Kasprzyk K, Dordelly LJ, Celli BR. The 6-min walk distance, peak oxygen uptake, and mortality in COPD. *Chest* 2007;**132**:1778—85.
23. American Thoracic Society Official Statement. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1995;**152**: S77—120.
24. Chhajed PN, Malouf MA, Tamm M, Spratt P, Glanville AR. Interventional bronchoscopy for the management of airway complications following lung transplantation. *Chest* 2001;**120**: 1894—9.
25. Susanto I, Peters JI, Levine SM, Sako EY, Anzueto A, Bryan CL. Use of balloon-expandable metallic stents in the management of bronchial stenosis and bronchomalacia after lung transplantation. *Chest* 1998;**114**:1330—5.